R E M A R K S

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Initially, Applicants wish to express their appreciation to the Examiner for discussing this application with the undersigned attorney in a personal interview on May 15, 1996. During the recent interview, the issues outstanding in connection with this application were discussed at some length. Final agreement with the Examiner on the outstanding issues was not reached; however, the Examiner agreed to fully consider the instant response and to reevaluate the patentability of the instantly claimed subject matter based upon the response. The substance of the recent interview is incorporated in the EXAMINER INTERVIEW SUMMARY RECORD prepared by the Examiner at the time of the interview and entered into the file as Paper No. 33. Again, the courtesy of the Examiner in granting the interview to the undersigned attorney is gratefully acknowledged.

In the most recent Official Action, the Examiner has stated:

> "Moreover, it should be noted that the claims are not limited to administration to humans."

In order to clarify the claims in this regard, Applicants are submitting herewith certain amendments to the claims. Thus, claim

31 is amended at line 1 to specify that the composition is for oral administration to humans. In respect to claim 32, directed to the method of use, Applicants have previously interpreted the meaning of the word "patient" to be limited to humans and Applicants believe that the conventional interpretation of this term in the USPTO is in agreement with such interpretation. However, in order to eliminate any question in this regard, the term "patient" in claim 32 is amended to read "human".

It is believed that the amendments effected in the claims will clarify the subject matter of the claims and further that these amendments do not raise any new issues in connection with the prosecution of the application and can clearly thus be entered by the Examiner.

The claims of the application stand rejected under the provisions of 35 U.S.C. 103 as being unpatentable over Deng (AQ) in view of Wang et al. (R) and Lin et al. (S). This ground of rejection is deemed to be untenable and is thus vigorously traversed by the Applicants. Applicants respectfully submit that the steps in reasoning necessary for the Examiner to reach a conclusion of obviousness under 35 U.S.C. 103 based upon these references is clearly unwarranted in the light of the teachings of these references and in the light of the evidence which is of record herein.

The composition of the present invention is an orally administrable composition for the treatment of malaria. Based upon the state of the art as it existed at the time of the present invention, Applicants respectfully submit that it cannot properly be said that such orally administrable composition would have been obvious to those skilled in the art.

The basic point upon which the Examiner hinges the argument of obviousness is that the oral administration of artemether would have been obvious in view of Lin et al.. Applicants cannot concur with the position taken by the Examiner in this regard. Arguments against the Examiner's position have been set forth in detail in Applicants' response to October 24, 1995 which arguments are incorporated herein by reference.

The Examiner, in the most recent Official Action contends that "intragastric gavage (i.g.) is highly suggestive of oral administration". It is respectfully requested, however, that the Examiner reconsider that argument in view of the fact that there is no link between the administration of an active agent administered to animals by intragastric gavage and an oral dosage form of combined active agents administered to humans. The Lin et al. reference literally says "oral" administration but correctly means "intragastric gavage". This has been made completely clear by Applicants' arguments of October 24, 1995.

The Lin et al. reference, according to the complete English translation which has been submitted to the Examiner, relates to the level of *in vivo* experimentation wherein a selected compound is tested in an animal test model indicative for treatment of the malaria disease. The results published in the reference proved the efficacy of the selected compound artemether against malaria within the framework of the conditions of a specific test model. Only one test model mentioned in the reference relates to treatment against malaria, c.f., Section 3: "The Effect of Artemether on Serum IgG in *Plasmodium* berghei Infected Mice" whereas the other test models relate to immunological aspects.

Interesting results established in one animal test model depend on the experimental conditions of the test model chosen, but allow no predictability regarding efficacy in other animal models. It is known that many active agents have proven to be effective in one model but fail in other animal models selected for testing. No predictability exists with respect to the efficacy in other test models and, moreover, there is no predictability with respect to the efficacy in humans even if a mode of administration is chosen which is related to the mode of administration in the animal test model.

With respect to artemether, this active species was known to be active against malaria in humans as of the priority date of the

present application. Moreover, other relevant information was also available at that date. As emphasized before, this active agent was known to be administrable to humans only by intramuscular injection of an oily liquid due to solubility problems. In this respect, note the Wernsdorfer Declaration presented with Applicants' response of January 17, 1995. Note that the Wernsdorfer Declaration makes it clear that as of the priority date of the present application, the state of the art was that artemether was recognized as being administrable only by the intramuscular route.

If these facts are interpreted together with the Lin et al. reference which teaches the efficacy of the same active agent in an animal model characterized by intragastric administration, one arrives at the following conclusions:

The fact that artemether was known to be effective in human beings at the date of the present invention, reveals that the art has progressed further and that the efficacy of this active antimalarial agent in other animal test models was also known. Therefore, other modes of administering this active agent to a test animal were known and available to the artisan. No guidance toward oral administration in view of the Lin et al. reference and no preference for oral dosage forms may therefore be derived from the

prior art. It will, then, be clear that the prior art does not suggest an oral dosage form containing the combined active agents artemether and benflumetol.

The relevant date to be considered is **August 8, 1990**, when the first Chinese priority application was filed, and not the earlier date in 1985 when the Lin et al. reference was published. In 1990, artemether was known to be administrable to humans by intramuscular injection as an oily suspension. This is the state of the art relevant to the artisan in 1990. At that time, he would no longer have considered a remote reference from 1985 being five years older which taught at an earlier stage of experimentation, a different mode of administration to animals. In the meantime, between 1985 and 1990, the efficacy of the artemether component in humans and certain advantages of the oily suspension as compared to other dosage forms have been established. The desirability of the oily suspension of the artemether component at the relevant date of the present application is a suggestion that the art-skilled would not have considered an oral dosage form wherein the same active agent is present as one of the active components.

Therefore, the experimental mode of administration of an individual component to animals disclosed in the older Lin et al. reference clearly fails to suggest the oral mode of administering the combined active agents to humans since a different mode of

administering one component to humans was, at that stage, firmly established in the art in more recent references.

Thus, the jump in reasoning of the Examiner from the teachings of the Lin et al. reference to a conclusion of obviousness of the instantly claimed bi-component orally administrable composition is indeed not warranted.

The attention of the Examiner is also respectfully directed to the Wernsdorfer Declaration filed with Applicants' response of January 17, 1995 and specifically to the conclusions of Dr. Wernsdorfer at page 6 of that Declaration. Note that Dr. Wernsdorfer concludes that as of the filing date of the present application, the suitability of artemether for inclusion in solid oral dosage forms was not known. He further concludes that as of that date, the antimalarial effect of a solid oral dosage form containing the combined agents artemether and benflumetol was unpredictable. He further concludes that it was unpredictable from the literature that the combination of benflumetol with artemether in the combined oral dosage form would render the insoluble compound artemether water soluble or absorbable in the gastro-intestinal tract. Finally, he concludes that it was also unpredictable that a combined dosage form would increase the solubility of the gastro-intestinal absorption of the component artemether. Dr. Wernsdorfer was and is clearly an expert in the art in question and was aware of the state of the art as it existed at the time of the present invention.

Had it been obvious to the art-skilled, based upon the Lin et al. disclosure that artemether was suitable for oral administration to humans, it is inconceivable to believe that the state of the art at that time would have remained intramuscular injection of an oily solution of artemether. It surely must be recognized that the route of choice by the art-skilled is oral administration and yet at that time, the art-skilled did not recognize the feasibility of the oral dosage form. Applicants respectfully submit that this belies the conclusion of the Examiner that the instantly claimed subject matter would have been obvious to the art-skilled at the time the present invention was made.

Based upon the foregoing, Applicants respectfully submit that the Examiner's rejection of the claims is untenable and that such rejection should be reconsidered and withdrawn. Applicants submit that the present application is in condition for allowance and such allowance is solicited.

Respectfully submitted,

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